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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,098	02/04/2000	Jeffrey Stack	AURO1330	8316

7590 04/23/2002

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EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/498,098	Applicant(s) STACK ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,50,55 and 60* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-28,30-40,50 and 60* is/are rejected.

7)☒ Claim(s) *16 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-40, 50 and 60 are pending in the application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 19-28, 31-37, 60, and additionally claims 17, 18, 30 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an activity in a cell, a method of regulating the concentration of a target protein in a cell, and a host cell comprising a nucleic acid sequence ***in vitro***, does not reasonably provide enablement for said methods and said cell ***in vivo***. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims as written read on both *in vitro* and *in vivo* embodiments. Although the specification discloses how the methods can be used *in vitro*, the state of the art of the production of transgenic animals at the time of filing was and continues to be unpredictable. For instance, it is well known in the art that the level and the specificity of expression of a transgene as well as the phenotype of a transgenic animal thus produced are greatly dependent on the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site of integration, etc. are all important factors in controlling the expression of the transgene. It is well known that the transgenic art is

unpredictable in regard to producing animals of different species which exhibit identical phenotypes due to expression of a transgene. For example, Wall (Theriogenology, Vol. 45, pages 57-68, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Overbeek ("Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98, 1994) states that considerable variation in the level of transgene expression occurs between founder animals (page 96, last paragraph).

In addition, the species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop similar phenotypes in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the phenotype of a theoretical transgenic animal was unpredictable at the time of filing and one of skill in the art could not readily predict that a transgenic animal would have the desired phenotype of interest.

The claims, as written, encompass transgenic non-human mammals to be used in a method of detecting an activity in a cell *in vivo*, a method of regulating the concentration of a target protein in a cell *in vivo*, and a host cell in the transgenic animal. The specification discloses possible methods of creating non-human transgenic. However, due to the examples stated above, the production of transgenic animals having the particular phenotype was unpredictable at the time of filing. One of skill in the art could not readily predict that any non-human transgenic animal would have the desired phenotype required to be useful for the methods claimed.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance in the specification, the absence of working examples for the methods claimed in all non-human organisms, the unpredictability of the art with respect to the expression of a transgene in all non-human mammals, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success. The specification does discloses how an ordinary artisan could attempt to make a transgenic animal, however there could not be a reasonable expectation of success.

Response to Arguments

Applicant's arguments filed 2/4/2002 have been fully considered but they are not persuasive.

Applicants argue that, "Although the production of particular transgenic animals with specific phenotypes may be to a certain extent unpredictable, ***the claims at issue*** are not directed

to methods of producing adult transgenic animals exhibiting a specific phenotype. By contrast the method claims are directed to methods of detecting activity in a cell, or regulating the concentration of a target protein in a cell, or the host cell itself." Applicants argue that the methods are fully enabled to the full scope of the claim by the specification as originally filed.

Applicants also argue that the references and arguments cited by the Examiner are directed towards difficulties of reproducibly creating phenotypes in different adult transgenic organisms. Applicants state that many of these difficulties are not directly related to the control of protein expression in a cell and are therefore irrelevant to the claims at issue.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., transgenic animals) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Given the broadest reasonable interpretation, the instant claims encompass methods in a cell, where the cell can be in vitro or in vivo since there is no limitation that the cell is in vitro. Methods drawn to cells in vivo encompass transgenic organisms (including insects, plants and animals) exhibiting a specific phenotype, that phenotype being the expression of the destabilized recombinant molecule. The production of transgenic organisms that reliably and accurately expresses the claimed recombinant molecules, which are required for all of the claimed methods, is unpredictable for the reasons set forth in the previous Office Action. Therefore, the rejection stands.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 recites the phrase, "A recombinant DNA molecule comprising a nucleic acid sequence **encoding for**;" (emphasis added). This recitation renders the claim indefinite because it is unclear how a nucleic acid sequence can be "encoding for" anything. Amendment of the claim to recite, for example, "a nucleic acid sequence encoding" would obviate this rejection.

It is believed that claim 50 is free of the prior art and amending the claim to obviate the rejection would render claim 50 allowable.

In view of the amendment, the rejection of claims 22, 24-28 and 31-37 under 35 U.S.C. second paragraph are withdrawn.

The arguments regarding the rejection of claim 23 is persuasive and the rejection under 35 U.S.C. second paragraph is withdrawn.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claim 38 is rejected under 35 U.S.C. 102(a) as being anticipated by Corish et al. (Protein Engineering 12 (12) 1035-1040. December, 1999).

Claim 38 is rejected under 35 U.S.C. 112, first paragraph as not being enabled as an in vivo method, but is enabled for an in vitro method. However, the instant claim is rejected under 35 U.S.C. 102(a) as the claimed method, as it pertains to cells in vitro, was known in the prior art.

Claim 38 is directed to a method of destabilizing a target protein in a cell comprising operatively coupling a target protein to a linear multimerized destabilization domain, wherein said destabilization domain is non cleavable by alpha-NH-ubiquitin protein endoproteases and comprises at least two copies of a destabilization domain.

Corish et al. discloses a method of destabilizing (i.e. decreasing the half-life) green fluorescent protein (GFP) in mammalian cells by operatively coupling a PEST domain to the C-terminus of GFP and a cyclin B1 destruction box to the N-terminus of said GFP (see abstract). The PEST domain and the cyclin B1 destruction box are capable of destabilizing GFP when individually coupled to GFP, but show an additive effect when both are operatively coupled to the target protein (see figure 2). The PEST domain and the destruction box act as destabilization domains and are not known to be cleavable by alpha-NH-ubiquitin protein endoproteases. The coupling of both the PEST domain and the destruction box to GFP is in essence coupling two copies of a destabilization domain (i.e. a linear multimerized destabilization domain) that is noncleavable by alpha-NH-ubiquitin protein endoproteases to a target protein. Therefore, Corish et al. clearly anticipate the method of claim 38.

Response to Arguments

Applicant's arguments filed 2/4/2002 have been fully considered but they are not persuasive.

Applicants argue that the reference does not anticipate the claimed invention because the claim is drawn to a "linear multimerized destabilization domain", which is defined in the specification on page 15, line 16 as, "at least two destabilization domains that are linearly coupled together." Applicants argue that the destabilization domains taught by Corish et al. are not linear multimerized domains because they "are not coupled together, but attached to either terminus of the protein of interest."

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., linear multimerization domains without intervening sequence between the multimerized domains) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

There is no support in the claim or in the specification that the destabilization domains must be multimerized in tandem without any intervening sequence. Therefore, the broadest reasonable interpretation of the claim encompasses a molecule comprising linearly coupled (not necessarily in tandem and without intervening sequence) destabilization domains wherein the destabilization domains are non-cleavable by α-NH-ubiquitin protein endoproteases and are coupled to a target protein. Corish et al. teaches such a molecule. For example, the molecule

taught by Corish et al. is a linear fusion protein comprising two destabilization domains (a PEST domain and a destruction box) coupled to a target protein (GFP). Therefore, the rejection of claim 38 stands.

Claim Rejections - 35 USC § 103

The arguments regarding the rejection of the claims under 35 U.S.C. 103 are deemed persuasive. Therefore the rejection of claims 38-40 and 50 under 35 U.S.C. 103(a) are withdrawn.

Allowable Subject Matter

6. Claims 16 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 1-15, 19-28, 31-40, 50 and 60 are rejected.

Claims 16 and 29 are objected to as depending on rejected claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
April 22, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER